

Anastomotic leakage and fistula after gastric and esophageal cancer surgery - a literature review

Dumitru Rădulescu⁽¹⁾, Cârțu Dan⁽¹⁾, Eugen Georgescu⁽¹⁾, Ion Georgescu⁽¹⁾, Valeriu Șurlin⁽¹⁾, Daniela Marinescu⁽¹⁾

⁽¹⁾University of Medicine and Pharmacy of Craiova, Department of Surgery

Abstract

The reduction of the incidence, detection and treatment of anastomotic leakage (AL) and fistula continues to preoccupy THE UPPER GI SURGICAL community. AL is not consistently reported in clinical trials, its occurrence reported variably, and its effects on morbidity and mortality insufficiently studied.

We extensively reviewed the most recent semiological data, methods of prevention and improvements in the management of secondary leakage and fistula of eso-gastric and eso-jejunal anastomosis after surgery for cancer.

Our aim was to find out the most important risk factors for the anastomotic leakage and to identify an optimal specific multidisciplinary management considering that anastomotic fistula occurs in critical patients where surgery is not the preferred approach in behalf of endoscopy management that can play an essential role in efficiency and safety, thus reducing mortality and costs.

To reduce the risk of anastomotic leakage and fistula, it is important to recognize high risk patients to customize management of each case.

Keywords: Anastomotic leak, anastomotic fistula, esophageal cancer, gastric cancer, risk factors

Introduction

In esophageal and gastric cancer surgery, as in all upper GI surgery the most dreaded surgical complication is the anastomotic leak, which conceptually represents the dehiscence or insufficiency of the anastomotic line that is leading to leakage of the intestinal content out of the lumen.

Depending on the anatomical region it may have a multitude of consequences, varying from an abscess that can solve spontaneously, to peritonitis or mediastinitis.

Clinical signs range from completely asymptomatic up to ileus, pain, fever or fatal sepsis [1].

There is a negative correlation with recurrence and long-term survival [2], and the quality of life [3].

The most important aspect that was always put into question in preventing the AL was the technical aspect of performing the anastomosis. Inverted sutures versus inverse sutures, types of stitches, single layer versus two layers and manual sutures have been carried out over time vs stapler [4]. Overall, these studies failed to demonstrate significant differences in efficacy [5].

Clinical studies demonstrated that anastomotic fistula cannot be accurately predicted by the operator, regardless of the patient's status and surgical technique used [6].

The result of these studies is affected by the biological factors underlying the pathophysiological process of healing anastomosis, therefore resulting the low impact of improved surgical technique on the incidence of anastomotic leakage.

Our aim was to perform a literature review in order to find the most important risk factors for leakage and identify the best management of this complication.

Methods:

We conducted a systematic review of the literature using the key words "anastomotic leak", "anastomotic fistula", "esophageal cancer", "gastric cancer", "semiology", "comorbidities", "risk factors". Of the 3832 possible references, we further screened for articles in English and published in indexed journals. After eliminating redundant publications and citations, only 52 articles remained.

Selected articles were reviewed for definition of anastomotic leak after esogastric cancer surgery, identifiable risk factors and management of the patient

We systematized data in the literature in definition of the anastomotic leakage, diagnosis, the influence of comorbidities and risk factors, specific and multidisciplinary management of each particularly and prevention methods.

Corresponding author: Valeriu Șurlin, MD, Ph.D, First Surgical Unit, University of Medicine and Pharmacy of Craiova, Department of Surgery. E-mail: vsurlin@gmail.com

Received October 09, 2019; **Accepted** November 28, 2019; **Mars** 05, 2020

Citation: Rădulescu D., Cârțu D., Georgescu E., Georgescu I., Șurlin V., Marinescu Daniela. Anastomotic leakage and fistula after gastric and esophageal cancer surgery - a literature review. *Journal of Surgery [Jurnalul de chirurgie]*. 2020; 16(1): 13-22

Copyright: © 2020 Rădulescu D., et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Definition and Classification

More than 40 definitions of anastomotic leakage have been found in literature [7].

Lack of consensus on how to define anastomotic leakage arises from the wide variety of clinical manifestations and the way they are managed.

Anastomotic leakage has been defined as leakage of the intestinal content from an anastomosis between two empty viscera, with outer luminal content either through the wound or the leakage site, or can be collected in the neighborhood of anastomosis causing fever, abscess, septicemia, metabolic disorders and or multiple organ failure

Leakage can be detected by imaging investigations, changing aspect of the fluid in the surgical drains or at the surgical reintervention [8].

Any local leakage in the anastomosis that has not clinical signs can be considered *subclinical* or minor leakage [9].

Radiological anastomotic leakage is defined as a leakage seen in the radiological examination without the patient showing clinical signs.

The term of minor and major leaks are related to clinical symptoms of anastomotic leakage. When a minor

leakage requires a change in surgical or medical management, is defined as a major one[10].

Classification - Clinical Criteria

There are currently a lot of anastomotic leakage classification systems, but the most commonly used is the one developed by Lerut et al. in Table 1[11].

The most serious form of anastomotic leak according to this system is that is caused by necrosis of a portion of anastomosis, reported between 0.5-3.2% [12].

Anastomotic lesions can be manifested subclinically by vague clinical signs with extravasation of the radiological and clinical images with signs of sepsis including fever, tachycardia, hypotension, tachypnea, leukocytosis and peritonitis [13].

Depending on the time of occurrence, the anastomotic leakage is divided into *early*, that occurs within the first 2-3 days due to defects of technique and *late*, that occur within 5-8 days and are usually formed due to ischemic changes in the anastomosis[14].

In addition to the division of anastomotic leakages into clinical and subclinical, a division has recently been made in intraperitoneal and extraperitoneal anastomotic leaks [15].

Table 1 - Lerut classification

I)	subclinical (passage of the methylene blue solution through the drain, without obvious radiological confirmation) - no intervention
II)	minor (radiologically proven fistula with minor clinical complications - inflammation of cervical wound, fever, leucocyte growth) - treat locally
III)	major (radiologically proven fistula with major clinical complications - major anastomosis with sepsis) - treated by percutaneous drainage or surgical reintervention
IV)	complete (endoscopically revealed intestinal necrosis) - reintervention is recommended

Anastomotic lesions that occur at the peritoneum are often accompanied by several clinical signs of peritonitis, most likely due to the large peritoneal surface [16]. On the other hand, extraperitoneal anastomotic leakage does not come into contact with the peritoneal surface that is innervated, that is why it presents an insidious debut [17].

Incidence

Anastomotic leakage has an incidence between 0-35% after esophagectomy and 2.7-12.3% after total gastrectomy, with significant variations of clinical severity, depending on the size of the cohort and the time elapsed from surgery [18].

In the cervical esophagectomy the leakage rate varies between 4.8% and 53% compared to thoracic anastomosis with a leakage incidence between 1.6% -16.1%, with mortality between 18-60% [19].

For gastrointestinal anastomosis, the fistula rate is between 1-3% and mortality may reach up to 50% [20].

Esophagectomy presents one of the highest mortality rates, perioperative mortality is 5%, but surgery for major postoperative complications has a mortality over 30% [21].

The rate of postoperative leaks is frequently used as a quality indicator of the surgical act.

Risk Factors

Surgery on the upper gastrointestinal tract is associated with a strong systemic inflammatory response both during and after surgery, so the patient needs adequate cardiopulmonary resources to resist metabolic requirements as a result of surgery.

NUTRITIONAL DEFFICIENCY

Patients with **nutrition deficiency** have an increased risk of complications and some studies show that preoperative weight loss is associated with an increased risk of anastomotic fistula. There are studies claiming that postoperative total parenteral nutrition can reduce overall complications of surgical intervention in malnourished patients [22]. Due to the preoperative administration of total parenteral nutrition, only one study of total pre-operative parenteral nutrition in ulcerative colitis patients undergoing colectomy was shown to be of benefit, proving that there was no improvement in the rate of the occurrence of anastomotic leakage. At the same time, there is an increasing number of evidence showing that enteral nutritional supplements reduce surgical complications [23]. Malnourished patients receiving immune food have been shown to have increased immunity and even improvement in postoperative clinical development, with no added benefit if administered to patients who are not malnourished [24], having the structure in addition to proteins and immune growth components that enhance the immune response (glutamine, arginine, N-3 fatty acids and ribonucleic acids). Although the rate of anastomotic leakage was not individually assessed, it is clear that lowering the rate of infection decreases the complications as well as the incidence of leakage.

SMOKING has been shown to be a risk factor in the development of anastomotic fistula, so studies of different types of gastrointestinal anastomosis have shown an increase in incidence four times as compared to non-smokers [26]. Quitting smoking in the short term has not been effective, but the latest recommendations involve quitting smoking for 4-8 weeks before surgery and throughout the healing period [26], so we can say that stopping smoking has an impact on postoperative complications and can be proposed as a mandatory stage in preoperative preparation.

STEROIDS. The use of steroids is described in numerous publications as an independent risk factor for altering healing. Long-term administration of high-dose steroids has been shown to impair intestinal healing, and systemic analysis has shown that steroids increase the rate of anastomotic leak [27].

NSAIDS. The use of non-steroidal anti-inflammatory drugs, in particular, of cyclooxygenase-specific (COX) -2 antagonists may contribute to an increase in anastomotic leak, because COX-2 inhibition may reduce collagen production and consequently affect the healing process. Initial evidence in 2009 showed an increase in the incidence of anastomotic leak from 3.3% to 15.1% [28]. A few years later was confirmed by a retrospective study with an incidence increase from 7.6% to 13.2% after NSAID use [29]. A recent meta-analysis has concluded that the association of anastomotic leakage with NSAIDs is erroneous, but that there is still concern about the use of NSAIDs [30].

PREOPERATIVE CHEMOTHERAPY is commonly used for esophageal cancers. Neoadjuvant chemotherapy did not show an increase in the incidence of anastomotic leak in esophageal surgery [31]. A study evaluating the time of esophagectomy after chemoradiation did not show any difference in previous or subsequent surgery (less than 8 weeks vs. more than 8 weeks) [32]. This study shows that the incidence of anastomotic leak is not influenced by the time elapsed since chemoradiation.

PREOPERATIVE RADIOTHERAPY It has also been proved to increase the risk of AL by triggering increased tissue fibrosis, resulting in changes in microvasculature resulting in a slowing of healing [33].

BLOOD TRANSFUSION Is considered a risk factor for anastomotic leakage and can be considered a surrogate marker for surrogate surgical procedures. Transfusion itself may increase surgical complications as a consequence of transfusion-related immunomodulation (TRIM) [34].

Surgical Technique

In conducting anastomosis on the gastrointestinal tract it is very important to correctly apply the surgical technique by preparing the patient preoperatively, avoiding anastomosis tension and ensuring the viability of the anastomotic partners.

Certain local tissue conditions can also increase the risk of anastomotic leakage, by infiltration of gastrointestinal cancers, regional infection, low tissue perfusion [35], and incompetent mucosal anastomosis approximation.

In spite of the impeccable technique put into practice and the vast experience of the operative physician, occasionally the anastomotic fistula cannot be anticipated, most of the time [36].

There has been a long discussion about the recommended manual or mechanical suture type, cervical or intrathoracic location, and the type of end-to-end anastomosis, latero-lateral questionable in restricted access such as the esophagus, still difficult to determine the superiority of a technique to the other.

The cervical location of anastomosis has a higher risk of fistula than intrathoracic localization [37].

There are currently 3 anastomosis techniques after the esophagectomy: hand suture, circular stapler, and linear semimechanic stapler that was successfully introduced by Collard et al., later popularized by Orringer et al [38]. Unlike the round lumen in manual and circular stapler, the triangular lumen created by latero-lateral anastomosis with a linear stapler is believed to create a better healing base and reduce the risk of strictures as demonstrated by non-randomized studies [39]. There are only a few retrospective studies that compared both methods in performing intrathoracic anastomosis, and in the case of linear stapler suture there was no reduction in the fistula rate, while stenosis formation was favorably influenced [40]. The only randomized study comparing the 3 intrathoracic anastomosis techniques was focused on late development of stricture, not evaluating the occurrence of anastomotic fistula [41].

Treatment

Patients who experience septic complications and anastomotic leakage should be transferred to intensive care and early haemodynamic support, intravenous fluid resuscitation, bowel rest in the early phase of treatment, and intravenous broad spectrum antibiotics.

In a study conducted by Kumar et al [42] on 14 intensive care units, the importance of antibiotics was demonstrated in a shorter time by the discovery that there was a decrease in survival of 7.6% for every one hour delay in antimicrobial administration.

Conservative treatment consists of parenteral nutrition, broad-spectrum antibiotics and minimal surgical drainage [43].

In recent years, endoscopic approach has been proposed, especially for late-onset anastomotic leakage in order to obtain defect repair through a minimally invasive approach. These therapeutic procedures include injection of fibrin adhesives, placement of endoscopic clips, suture devices, insertion of stents and vacuum endoluminal devices.

Prior to treatment, **endoscopic debridement** is required to remove the pus and tissue debris from inside and around the necrotic cavity using endoluminal cleansing and suction devices. Additionally, washing with hydrogen peroxide [44] is performed in the cavity and complete drainage of the mediastin, pleura or peritoneal cavity collections.

Fibrin adhesives have begun to be increasingly used in various surgical fields because of their hemostatic uniqueness and adhesive property. They are synthesized from freshly frozen plasma, contain fibrinogen, coagulation factor XIII, thrombin, ionized calcium and fibronectin. The fibrin adhesive is solidified in a rubber-like white mass with strong adhesive properties. Injection of fibrin adhesives succeeded in healing fistulas with a diameter of less than 5 mm, with a 37% success rate. Studies have shown that the application of fibrin adhesives to the suture lines would reduce the incidence of leakage [45].

Endoses have a widespread use in endoscopy, especially for mechanical haemostasis in post-procedural bleeding.

Endoluminal closures of iatrogenic esophageal perforations have been reported with clips (through the scope, over the scope) and endoluminal suture techniques [46].

A new type of OTSC (Ovesco Endoscopy, Tübingen Germany) clips was developed, consisting of a Nitinol clip loaded at the end of the endoscope, allowing it to catch a large amount of tissue to compress and close the lesion edges [47]. A recent meta-analysis on the end-piece technique reviewed the literature and concluded that the use of endoscopes on the esophagus is useful when the defect is less than 20 mm, but surgical intervention is recommended if the defect is older than 24 hours, is greater than 20 mm or the leakage of the mediastinum is highlighted [48]. Verlaan et al. performed a meta-analysis on various endoscopic closure systems and found that the authors reported a successful endoclips closure in the scope of 90.2% and over the scope of 87.8% [49].

Endoscopic VAC (Endo-SPONGE, B. Braun Medical Ltd) endoscopic endoscopic device is a method originally introduced in the 90's. The system is based on a negative pressure applied to wounds with a tube inserted into a polyurethane foam having consequences arteriolar dilation, stimulation of granulation tissue formation, and closure of the fistula [50]. This method is applied to large fistulae in thoracic anastomosis. After the endoscopic debridement of the wound cavity, a sponge is cut to the estimated endoscope size, fixed to the distal end of the tube is applied to the necrotic cavity and continuous aspiration is started, the procedure is repeated twice a week [51]. Vacuum therapy has been investigated demonstrating its usefulness especially in patients with esophageal anastomotic leakage [52]. A retrospective study by Menningen, comparing 30 patients who underwent endoscopic stent therapy with 15 patients undergoing vacuum treatment, achieved promising results with higher success rates in the latter [53]. Vacuum therapy used as a single agent or in combination with esophageal stent placement is an option for patients with anastomotic leakage. The endoscopic VAC system allows a regular

visualization of the anastomotic defect, infected cavity debridement, and septic outbreak control [54].

The use of **endoluminal esophageal stents** to treat esophageal anastomotic leakage is not a new concept in surgery. The first successful experience was that described by Szmonds in 1887 using ivory and silver prostheses [55]. In 1914, Guizzi was the first to place esophageal "tubes" under direct view to alleviate esophageal obstructions [56]. Cletsin modified a French design by Mousseau and Barbin by developing a polyethylene stent for inoperable malignant strictures, thus managing to maintain oral intake, but the use of this stent was limited due to the difficulty of insertion, migration and extraction. With the development of technology, self-expanding stents became available in the 1990s, being manufactured using laser methods designed to exert self-expansion forces up to a fixed diameter, made of steel alloys (cobalt, nickel, chromium) high radial or nitinol (nickel and titanium) which allows low flexibility with less radial forces [57].

The self-expanding metal stents were reserved only for patients requiring palliative therapy due to lesions associated with extraction, including irreparable, life-threatening leaks. To avoid these complications, second-generation metallic stents have been developed that are covered by silicone, polyurethane or other polymers [58].

The emergence of biomaterials has led to the development of a silicone-coated occlusive plastic prosthesis with a design that allows easy insertion and gives it increased esophageal lumen sleeve capacity [59]. These non-metallic endoprotheses have the advantage that they can be replaced or removed over a longer period without affecting the esophagus, but the migration incidence is similar to that of coated metallic stents [60].

In cervical leakage, surgical treatment consists of reopening the cervicotomy, drainage and insertion of a Pezzer catheter, the healing being calibrated by the nasogastric tube which is left in place throughout the healing period.

Objectives of management vary according also to the size of the leakage and extent of local inflammation.

- in the absence of severe local infection or ischemia, anastomosis is augmented by suture;

- in the presence of a mechanical strain or a small ischemic lesion, without the presence of signs of regional inflammation, anastomosis can be restored, but there is a new risk of anastomotic leakage [61];

- in the dehiscence less than one-third of the circumference of the anastomosis, a transanastomotic intubation with a T tube accompanied by endoluminal continuous irrigation with a nasogastric tube [62] is performed.

- when the anastomotic dehiscence is greater than half the circumference of the anastomosis or when the intestine is necrotic, it opts either for the discontinuation of the anastomosis in combination with the esophagostomy for intrathoracic esogastro-anastomosis or for the intubation of the esophagus with the exteriorization and the transformation of the Roux arm into the terminal jejunostomy; it is a radical and aggressive but short-lived life-saving solution [63]

Mortality varies depending on the percentage, being lower in the centers with the possibility of performing surgery to save the patient, but in order to reduce these differences it is recommended to optimize the management of postoperative complications.

Although the neoplastic state determines a high risk of mortality comprising patient's risk factors, the stage of the tumor, surgical technique, the large variations in major surgery mortality are given by the differences in patient's salvage rate [64].

Lower mortality centers have more possibilities for surgical reintervention in order to save the patient's life, but this consideration does not yet have a clear impact on survival. In order to reduce the differences between centers, it is advisable to optimize the management of postoperative complications in hospitals with increased figures of mortality [65].

Preventive Measures

Physical therapy to increase cardiopulmonary function, improved nutritional status, and preoperative oxygen optimization are recommended to improve preoperative physical condition [66].

ERAS protocols

Preoperative preparation according to the ERAS protocol in gastric and esophageal cancer surgery, which involves carbohydrate loading, results in decreased protein degradation and improves postoperative recovery with decreased anastomotic leakage.

The ERAS protocol in gastric and esophageal cancer surgery requires pre-operative patients to have a solid diet until the day before surgery and to drink 500ml of carbohydrate-rich liquids (18g carbohydrate per 100ml Arginaid water - Nestle Health Science Japan) after dinner, and on the day of the operation, another 250ml was drunk at least 3 hours before anesthesia. An antibiotic (Cefazolin) is administered before the skin incision, then every 3 hours, ending with an infusion after surgery. Administration of intraoperative fluids is decided by the anesthetist, so as to avoid overloading with sodium and fluids. The nasogastric aspiration probe is inserted before surgery and removed at 3 hours after surgery, unless there are signs of bleeding. On the first day of surgery, peripheral parenteral nutrition assumes a total of 2000 ml glucose containing 7.5% glucose and vitamins, followed by 7.5% glucose doses dropping to 1500, 1000 and 500 ml respectively on day two, the third and fourth of the operation. Unlike conventional training, patients are allowed from day one to use clear fluid on the second day, a liquid diet, which is intensified to a soft diet within 3 days [67].

Carbohydrate loading is an important component of the ERAS protocol, having the benefit of avoiding protein degradation and improving postoperative recovery. Carbohydrate loading accentuates intestinal peristalsis showing an adverse effect on the anastomotic site, especially after surgery on the upper gastrointestinal tract [68].

The incidence of anastomotic leakage of 0.8% is as low as that reported in previous studies (0.8-1.9%), or even less than that of eligible subjects of the historical cohort (1.7%) [69]. Yamada et al. [70] evaluated the value of ERAS protocols in a large volume Japanese center and also reported a decrease in the incidence of anastomotic leakage (1.1-1.5%).

Despite these findings, further studies are needed to demonstrate the feasibility of ERAS protocols in fragile and advanced cancer patients.

The intestinal microflora has an important role in intestinal healing, a role that has been known for over 60 years, and this has been demonstrated indirectly through numerous studies that involved antibiotic administration with examination of the fistula rate in both animals and humans. Among the first studies, Isadore Cohn performed an intestinal anastomosis in dogs, devascularizing the anastomotic segment until ischemia was highlighted; of a group of dogs were given antibiotics and the other batch of saline solutions directly at the site of anastomosis by placing a proximal feeding tube of anastomosis. Dogs treated with antibiotics demonstrated normal healing and a remission of ischemia, while dogs treated with salt solutions showed leakage and peritonitis. Subsequently, numerous animal studies and clinical trials have shown that unabsorbable oral antibiotics decrease but do not eliminate anastomotic leakage rates, and these studies demonstrate that microbes play a special role in anastomotic leakage [71].

Currently, surgeons do not regularly apply non-resorbable oral antibiotics as a prophylactic measure to prevent anastomotic leakage [72], continuing to eliminate microbes as agents causing anastomotic leakage, due to a lack of studies clearly demonstrating the role of intestinal microflora in the onset of infective complications.

A new understanding of intestinal microflora in the influence of health and the evolution of various diseases may have an increased influence on the methods of preparing the intestine for anastomosis.

The process of creating an anastomosis significantly alters the intestinal microflora in the anastomosis. Recent studies show that the presence of certain strains of specific bacteria (*Pseudomona aeruginosa*, *Enterococcus faecalis*) and low microbial diversity are correlated with the occurrence of fistula [73].

Although no clear details are known, the intake of bacteria in healing and the development of anastomotic complications is likely to be significant.

The mechanism of bacteria in the appearance of fistulas is their ability to produce collagen degradation that can lead to damage intestinal tissue about 7 times more than intestinal collagenase. Bacterial collagenases are more likely to alter healing than host tissue enzymes alone [74]. Although efforts made to perform a preoperative antisepsis, these collagenase-producing organisms persist in the anastomotic sites [75]. The poor results in the intestinal antisepsis approach are based regarding data from the literature of about 50 years, which are outdated and missing data, about intestinal microbes, such as microbial flora structure, phenotype, proteome and metabolome [76].

The intestinal bacterial flora of certain species and the low microbial diversity of the anastomosis correlate with the appearance of the fistula, the mechanism being the production of collagen degradation of collagen, which damages the intestinal tissue 7 times more than the intestinal collagenase.

Non-absorbable oral antibiotics, as a prophylactic measure to prevent anastomotic leakage, decrease, but do not eliminate anastomotic leakage rates, demonstrating that microbes play an important role in anastomotic leakage.

Ischemic conditioning of the stomach.

Since 1990, methods of preventing anastomotic leakage after eso-gastric cancer surgery have been initiated in Japan using stomach coil embolization techniques [77]. This technique is performed two weeks before anastomosis is performed and involves access to the femoral artery, celiac trunk artery and embolization of most stomach arteries, sparing the right gastroepiploic artery. The left gastric artery was embolized in all studies. All studies that have been performed on preoperative arterial embolization have been nonrandomized and have demonstrated that this procedure is feasible and safe [78]. Measurements of the stomach perfusion at the time of esogastric anastomosis showed that preoperative arterial embolization resulted in a lower decrease in blood flow from the stomach compared to patients who did not apply this procedure [79].

Patients with preoperative arterial embolism had a lower anastomotic leakage rate than the control group with minimal adverse effects such as abdominal pain, nausea, vomiting, which were treated conservatively.

This technique is useful, provided that patients who can effectively benefit from anastomotic leakage and severity are identified [80].

Staplers using bioabsorbable staple fiber reinforcing material have begun to be used, and studies have shown that they are safe, but there is no convincing evidence of lower anastomotic leakage rates, but the potential for reducing anastomotic strictures [81].

The use of **fibrin adhesives** has been studied in obesity surgery to reduce the incidence of digestive anastomotic leakage, remaining a popular method in intestinal anastomosis despite the lack of evidence of comparison [82].

Leakage test. After the esophageal and gastric anastomosis, an intraoperative evaluation known as the "leakage test" can be performed by superior digestive endoscopy if the anastomosis is proximal enough for accessibility, being examined for bleeding on the stapler suture line or abnormalities union, anastomotic integrity being verified by submerging the intestine into the fluid and examining the bubbles caused by insufficient lumen closure. Recent studies have shown that the intraoperative endoscopic assessment of the anastomosis line is safe, feasible and able to detect the presence of bleeding and anomalies, and this method may reduce anastomotic complications, and there is no study demonstrating any secondary damage to the procedure.

Knowing these advantages, the "leakage test" does not prevent and predict the leakage, it is just a way of verifying the tightness of the anastomosis and prevents fistulas by lack of technique, those that are expressed in the first postoperative days and are not due to scarring.

Type of anastomosis. Handsewn and circular stapler anastomosis create a round-shaped lumen, but side-by-side anastomosis with a linear stapler would create a better healing base and lower the risk of anastomotic leakage or stricture.

Pain control by paravertebral epidural analgesia plays a role in rapid postoperative mobilization and decrease the risk of pneumonia.

Improvement of nutritional status. Undernourished patients who are given "growth-enhancing" proteins and components show a decrease in the complication rate, especially the incidence of fistulas.

Although there are currently no drugs or techniques to improve the healing of gastrointestinal anastomosis, many ongoing studies investigate other therapeutic options such as

topical application or systemic delivery of growth factors directed to the stages of intestinal healing [83].

Conclusions

Anastomotic fistula remains a major complication after esophageal surgery cannot be accurately predicted by the operator regardless of the state of the pace and the surgical technique used.

For early diagnosis, a high suspected index is important to help recognize high-risk patients by tailoring specific and multidisciplinary management, as delay in diagnosis may compromise prognosis.

Often, anastomotic leakage occurs in critical patients where surgery is not the preferred approach of first intention, so in endoscopy management algorithm can play an essential role in efficiency and safety compared to surgical treatment, thus reducing mortality and costs.

If anastomotic leakage becomes life-threatening requires emergency surgery along with all intensive care measures.

Prevention of anastomotic leakage is very important, but precocity and management optimization decrease the consequences and can increase survival.

Despite the efforts to reduce the risk of anastomotic leak, it cannot be avoided completely and may have severe consequences and may be difficult to manage.

To reduce the risk of an anastomotic leakage and fistula, it is very important to recognize high-risk patients and thus to customize the specific and multidisciplinary management of each case.

Conflict of Interest

Authors have no conflict of interest to disclose.

References

1. Caulfield H, Hyman NH. (2013) Anastomotic leak after low anterior resection: a spectrum of clinical entities. *JAMA Surg*, 148(2): 177-82.
2. Markar S, Gronnier C, Duhamel A, et al. (2015) The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. *Ann Surg*, 262: 972-80.
3. Schaheen L, Blackmon SH, Nason KS. (2014) Optimal approach to the management of intrathoracic esophageal leak following esophagectomy: a systematic review. *Am J Surg*, 208(4): 536-43.
4. Chen C. (2012) The art of bowel anastomosis. *Scand J Surg*, 101(4): 238-40.
5. Nandakumar G, Stein SL, Michelassi F. (2009) Anastomoses of the lower gastrointestinal tract. *Nat Rev Gastroenterol Hepatol*, 6(12): 709-16.
6. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. (2009) Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis*, 24(5): 569-76.
7. Bruce J, Russell EM, Mollison J, et al. (2001) The measurement and monitoring of surgical adverse events. *Health Technol Assess*, 5(22): 1-194.

8. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. (2001) Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg*, 88(9): 1157-68.
9. Peel AL, Taylor EW. (1991) Proposed definitions for the audit of postoperative infection: a discussion paper. *Surgical Infection Study Group. Ann R Coll Surg Engl*, 73: 385-8.
10. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. (2001) Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg*, 88(9): 1157-68.
11. Lerut T, Coosemans W, Decker G, De Leyn P, Nafteux P, van Raemdonck D. (2002) Anastomotic complications after esophagectomy. *Dig Surg*, 19: 92-8.
12. Ferri LE, Law S, Wong KH, et al. (2006) The influence of technical complications on postoperative outcome and survival after esophagectomy. *Ann Surg Oncol*, 13: 557-64.
13. Rickles, Aaron S. et al. (2014) Non-operative treatment of anastomotic leaks: Current and investigational therapies. *Seminars in Colon and Rectal Surgery*, 25(2): 67-73
14. J. Zehetner, S.R. DeMeester, E.T. Alicuben, D.S. Oh, J.C. Lipham, J.A. Hagen, et al. (2015) Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after Esophagectomy. *Ann. Surg*, 262(1): 74-78.
15. Phitayakorn R, Delaney CP, Reynolds HL, et al. (2008) Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. *World J Surg*, 32(6): 1147-1156.
16. Galandiuk S. (2005) To drain or not to drain. *Ann Surg*, 241(1): 14-15.
17. Y. Haga, T. Beppu, K. Doi, F. Nozawa, N. Mugita, S. Ikei, et al. (1997) Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. *Crit. Care Med*, 25(12): 1994-2000.
18. Rutegard M, Lagergren P, Rouvelas I, et al. (2012) Intrathoracic anastomotic leakage and mortality after esophageal cancer resection: a population-based study. *Ann Surg Oncol*, 19: 99-103.
19. Merritt RE, Whyte RI, D'Arcy NT, et al. (2011) Morbidity and mortality after esophagectomy following neoadjuvant chemoradiation. *Ann Thorac Surg*, 92: 2034-40.
20. Donatelli G, Dhumane P, Perretta S, Dallemagne B, Vix M. (2012) Endoscopic placement of fully covered self-expanding metal stents for management of postoperative foregut leaks. *J Minim Access Surg*, 8: 118-124.
21. Armitage M, Eddleston J, Stokes T, Guideline Development Group. (2007) Recognising and responding to acute illness in adults in hospital: summary of NICE guidance. *BMJ*, 335(7613): 258-259.
22. Turrentine FE, Denlinger CE, Simpson VB, et al. (2015) Morbidity, mortality, cost, and survival estimates of gastrointestinal anastomotic leaks. *J Am Coll Surg*, 220(2): 195-206.
23. Salinas H, Dursun A, Konstantinidis I, et al. (2012) Does preoperative total parenteral nutrition in patients with ulcerative colitis produce better outcomes? *Int J Colorectal Dis*, 27(11): 1479-1483.
24. Klek S, Kulig J, Sierzega M, et al. (2008) The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. *Ann Surg*, 248(2): 212-220.
25. Baucom RB, Poulouse BK, Herline AJ, Muldoon RL, Cone MM, Geiger TM. (2015) Smoking as dominant risk factor for anastomotic leak after left colon resection. *Am J Surg*, 210(1): 1-5.
26. Jung KH, Kim SM, Choi MG, et al. (2015) Preoperative smoking cessation can reduce postoperative complications in gastric cancer surgery. *Gastric Cancer*, 18(4): 683-690.
27. Eriksen TF, Lassen CB, Gögenur I. (2014) Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: a literature survey. *Colorectal Dis*, 16(5): O154-O160.
28. Holte K, Andersen J, Jakobsen DH, Kehlet H. (2009) Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. *Br J Surg*, 96(6): 650-654.
29. Gorissen KJ, Benning D, Berghmans T, et al. (2012) Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. *Br J Surg*, 99(5): 721-727.
30. Bhangu A, Singh P, Fitzgerald JE, Slessor A, Tekkis P. (2014) Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies. *World J Surg*, 38(9): 2247-2257.
31. Kumagai K, Rouvelas I, Tsai JA, Mariosa D, Klevebro F, Lindblad M, et al. (2014) Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. *Br J Surg*, 101(4): 321-338.
32. Kim JY, Correa AM, Vaporciyan AA, et al. (2012) Does the timing of esophagectomy after chemoradiation affect outcome? *Ann Thorac Surg*, 93(1): 207-212;
33. Iyer S, Balasubramanian D. (2012) Management of radiation wounds. *Indian J Plast Surg*, 45: 325-31.
34. Vamvakas EC, Blajchman MA. (2007) Transfusion-related immunomodulation (TRIM): an update. *Blood Rev*, 21: 327-48.
35. Patil PK, Patel SG, Mistry RC, Deshpande RK, Desai PB. (1992) Cancer of the esophagus: esophagogastric anastomotic leak: a retrospective study of predisposing factors. *J Surg Oncol*, 49: 163-7.
36. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. (2009) Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis*, 24(5): 569-76.

37. Price TN, Nichols FC, Harmsen WS, Allen MS, Cassivi SD, Wagle DA et al. (2013) A comprehensive review of anastomotic technique in 432 esophagectomies. *Ann Thorac Surg*, 95: 1154-60.
38. Orringer MB, Marshall B, Iannettoni MD. (2000) Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. *J Thorac Cardiovasc Surg*, 119: 277-88.
39. Kondra J, Ong SR, Clifton J, Evans K, Finley RJ, Yee J. (2008) A change in clinical practice: a partially stapled cervical esophagogastric anastomosis reduces morbidity and improves functional outcome after esophagectomy for cancer. *Dis Esophagus*, 21: 422-9.
40. Price TN, Nichols FC, Harmsen WS, Allen MS, Cassivi SD, Wagle DA et al. (2013) A comprehensive review of anastomotic technique in 432 esophagectomies. *Ann Thorac Surg*, 95: 1154-60.
41. Wang WP, Gao Q, Wang KN, Shi H, Chen LQ. (2013) A prospective randomized controlled trial of semi-mechanical versus hand-sewn or circular stapled esophagogastric anastomosis for prevention of anastomotic stricture. *World J Surg*, 37: 1043-50.
42. Kumar A, Roberts D, Wood KE, et al. (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*, 34(6): 1589-1596.
43. Hyman NH. (2009) Managing anastomotic leaks from intestinal anastomoses. *Surgeon*, 7: 31-5.
44. Chopra SS, Mrak K, Hünerbein M. (2009) The effect of endoscopic treatment on healing of anastomotic leaks after anterior resection of rectal cancer. *Surgery*, 145: 182-8.
45. Higa KD, Boone KB, Ho T. (2000) Complications of the laparoscopic Roux-en-Y gastric bypass: 1,040 patients—what have we learned? *Obes Surg*, 10: 509-513.
46. Baron TH, Wong Kee Song LM, Zielinski MD, et al. (2012) A comprehensive approach to the management of acute endoscopic perforations. *Gastrointest Endosc*, 76: 838-59.
47. Schurr MO, Hartmann C, Ho CN, et al. (2008) An over-the-scope clip (OTSC) system for closure of iatrogenic colon perforations: results of an experimental survival study in pigs. *Endoscopy*, 40: 584-8.
48. Yilmaz B, Unlu O, Roach EC, et al. (2015) Endoscopic clips for the closure of acute iatrogenic perforations: Where do we stand? *Dig Endosc*, 27: 641-8.
49. Furukawa K, Miyahara R, Funasaka K, et al. (2016) Endoscopic Closure of Duodenal Perforation with the Over-the-scope-clipping System. *Internal Medicine*, 55(21): 3131-3135.
50. Morykwas MJ, Argenta LC, Shelton-Brown EI, et al. (1997) Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. *Annals Of Plastic Surgery*, 38: 55-62.
51. Wedemeyer J, Schneider A, Manns MP, et al. (2008) Endoscopic vacuum-assisted closure of upper intestinal anastomotic leaks. *Gastrointestinal Endoscopy*, 67: 708-11.
52. Siersema PD, de Wijkerslooth LR. (2009) Dilatation of refractory benign esophageal strictures. *Gastrointestinal Endoscopy*, 70: 1000-12.
53. Hernandez LJ, Jacobson JW, Harris MS. (2000) Comparison among perforation rates of Maloney, balloon and Savary dilatation of esophageal strictures. *Gastrointestinal Endoscopy*, 51: 460-2.
54. Wedemeyer J, Schneider A, Manns MP, et al. (2008) Endoscopic vacuum-assisted closure of upper intestinal anastomotic leaks. *Gastrointestinal Endoscopy*, 67: 708-11.
55. Symonds CJ. (1887) The treatment of malignant stricture of the oesophagus by tubage or permanent catheterism. *Br Med J*, 1: 870-3.
56. Guisez J. (1914) De l'intubation caouchoutée oesophienne. *Presse Med*, 22: 85.
57. Chan AC, Shin FG, Lam YH, et al. (1999) A comparison study on physical properties of self-expandable esophageal metal stents. *Gastrointest Endosc*, 49: 462-5.
58. Ramirez FC, Dennert B, Zierer ST, et al. (1997) Esophageal self-expandable metallic stents—indications, practice, techniques, and complications: results of a national survey. *Gastrointest Endosc*, 45: 360-4.
59. Decker P, Lippler J, Decker D, et al. (2001) Use of the Polyflex stent in the palliative therapy of esophageal carcinoma: results in 14 cases and review of the literature. *Surg Endosc*, 15: 1444-7.
60. Gelbmann CM, Ratiu NL, Rath HC, et al. (2004) Use of self-expandable plastic stents for the treatment of esophageal perforations and symptomatic anastomotic leaks. *Endoscopy*, 36: 695-9.
61. León-Espinoza CA, Bordu S, Lopez-Sebastian J, Muñoz-Fornier E, Morera-Ocón F, Sabater-Orti L, Camps-Vilata, Ortega-Serrano J. (2014) What guidelines tell us about acute pancreatitis, a review of the last international guidelines. *Central European Journal of Medicine*, (9): 588-593.
62. Parc Y, Frileux P, Dehni N, Ollivier J, Tiret E, Parc R. (2003) Réinterventions pour complications infectieuses intrapéritonéales postopératoires. Paris: Elsevier Masson, 40-080.
63. E. Girard, M. Messenger, A. Sauvanet, S. Benoist, G. Piessen, J.-Y. Mabrut, C. Mariette (2014) Anastomotic leakage after gastrointestinal surgery: Diagnosis and management. *Journal of Visceral Surgery*, 151(6): 441-450.
64. T. Hofer, R. Hayward. (1996) Identifying poor quality hospitals: can hospital mortality rates detect quality problems for medical diagnoses? *Med. Care*, 34(8): 737-753.
65. A.M. Almoudaris, R. Mamidanna, A. Boffle, P. Aylin, C. Vincent, O. Faiz, et al. (2013) Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England. *JAMA Surg*, 148(3): 272-276.

66. van Adrichem EJ, Meulenbroek RL, Plukker JT, Groen H, van Weert E. (2014) Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. *Ann Surg Oncol*, 21: 2353-60.
67. Sugisawa N, Tokunaga M, Makuuchi R, et al. (2016) A phase II study of an enhanced recovery after surgery protocol in gastric cancer surgery. *Gastric Cancer*, 19: 961-7.
68. Awad S, Varadhan KK, Ljungqvist O, Lobo DN. (2013) A meta-analysis of randomised controlled trials on preoperative oral carbohydrate treatment in elective surgery. *Clin Nutr*, 32: 34-44.
69. Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, et al. (2014) Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. *J Clin Oncol*, 32: 627-33.
70. Yamada T, Hayashi T, Aoyama T, Shirai J, Fujikawa H, Cho H, et al. (2014) Feasibility of enhanced recovery after surgery in gastric surgery: a retrospective study. *BMC Surg*, 14: 41.
71. Nelson RL, Gladman E, Barbateskovic M. (2014) Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev*, 5: CD001181.
72. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, et al. (2015) Nationwide analysis of outcomes of bowel preparation in colon surgery. *J Am Coll Surg*, 220(5): 912-20.
73. van Praagh JB, de Goffau MC, Bakker IS, et al. (2015) Intestinal microbiota and anastomotic leakage of stapled colorectal anastomoses: a pilot study. *Surg Endosc*, 30(6): 2259-65.
74. Shogan BD, Belogortseva N, Luong PM, et al. (2015) Collagen degradation and MMP9 activation by *Enterococcus faecalis* contribute to intestinal anastomotic leak. *Sci Transl Med*, 7(286): 286ra68.
75. Ohigashi S, Sudo K, Kobayashi D, et al. (2013) Significant changes in the intestinal environment after surgery in patients with colorectal cancer. *J Gastrointest Surg*, 17(9): 1657-64.
76. Bartlett JG, Condon RE, Gorbach SL, et al. (1978) Veterans administration cooperative study on bowel preparation for elective colorectal operations: impact of oral antibiotic regimen on colonic flora, wound irrigation cultures and bacteriology of septic complications. *Ann Surg*, 188(2): 249-54.
77. Isomura T, Itoh S, Endo T, et al. (1999) Efficacy of gastric blood supply redistribution by transarterial embolization: preoperative procedure to prevent postoperative anastomotic leaks following esophagoplasty for esophageal carcinoma. *Cardiovasc Interv Radiol*, 22: 119-23.
78. Diana M, Hubner M, Vuilleumier H, et al. (2011) Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. *Ann Thorac Surg*, 91: 1546-51.
79. Farran L, Miro M, Alba E, et al. (2011) Preoperative gastric conditioning in cervical gastropasty. *Dis Esophagus*, 24: 205-10.
80. Aristotelis Kechagias, Peter S.N. van Rossum, Jelle P. Ruurda, Richard van Hillegersberg. (2016) Ischemic Conditioning of the Stomach in the Prevention of Esophagogastric Anastomotic Leakage After Esophagectomy Review Article. *The Annals of Thoracic Surgery*, 101(4): 1614-1623.
81. Knapps J, Ghanem M, Clements J, Merchant AM. (2013) A systematic review of staple-line reinforcement in laparoscopic sleeve gastrectomy. *JSLs*, 17(3): 390-399.
82. Lee MG, Provost DA, Jones DB. (2004) Use of fibrin sealant in laparoscopic gastric bypass for the morbidly obese. *Obes Surg*, 14(10): 1321-1326.
83. Rijcken E, Sachs L, Fuchs T, Spiegel HU, Neumann PA. (2014) Growth factors and gastrointestinal anastomotic healing. *J Surg Res*, 187(1): 202-210.